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# Aerobic capacity exercise efficiency following aerobic and resistance training improve metabolic syndrome in individuals with type II diabetes

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## ABSTRACT (278)

**Introduction.** The simultaneous presence of type 2 diabetes (T2D) and metabolic syndrome exacerbates mortality risk. While exercise is often recommended for those with T2D, few studies have examined the effect of combining (AER+RES) aerobic (AER) and resistance (RES) training for individuals with T2D and metabolic syndrome.

**Methods.** We examined 9 months of AER, RES, and AER+RES training commensurate with physical activity guidelines in individuals with T2D (N=262, 63% female, 44% black). The primary outcome was change in metabolic syndrome at follow-up (mean, 95% CI). Secondary outcomes included maximal cardiorespiratory fitness ( $VO_{2peak}$  and time-to-exhaustion (TTE)) and exercise efficiency calculated as the slope of the line between ventilatory threshold, respiratory compensation, and maximal fitness. General linear models and bootstrapped Spearman correlations were used to examine changes in metabolic syndrome and exercise efficiency.

**Results.** We observed a significant decrease in metabolic syndrome (*p-for-trend*, 0.003) for AER (-0.59, 95% CI -1.00, -0.21) and AER+RES (-0.79, 95% CI -1.40, -0.35); both being significant ( $P \leq 0.02$ ) vs. Control (0.26, 95% CI -0.58, 0.40) and RES (-0.13, 95% CI -1.00, 0.24). Our observed decrease in metabolic syndrome was mediated by significant improvements in exercise efficiency for the AER and AER+RES training groups ( $P < 0.05$ ), which was more strongly related to TTE ( $r = -0.38$ , 95% CI, -0.55, -0.19) than  $VO_{2peak}$  ( $r = -0.24$ , 90% CI, -0.45, -0.01). Accordingly,  $VO_{2peak}$  increased by 5-6%, while TTE increased by 25-30%.

**Conclusion.** Aerobic and AER+RES training significantly improves metabolic syndrome in patients with T2D and appears to be mediated by improved exercise efficiency resulting in a greater TTE vs. increase in  $VO_{2peak}$ . This observation may be useful in reconciling the results of epidemiology vs. clinical data when interpreting improved exercise capacity.

**Key Words.** Metabolic syndrome, aerobic training, resistance training, exercise efficiency, Metabolic Equivalents (METs)

## INTRODUCTION

It is well recognized that metabolic syndrome is an independent risk factor for cardiovascular disease, diabetes, cancer and all-cause mortality.<sup>1</sup> More importantly is the observation that individuals with type 2 diabetes (T2D) who present with coexisting metabolic syndrome are not only at a higher risk for respective morbidities, but show additional risk for each accrued metabolic syndrome component feature than those without T2D.<sup>2,3</sup> ENREF3 Given the system wide physiological effects associated with exercise training, the continued advocacy for exercise training is of paramount importance for individuals presenting with T2D and metabolic syndrome simultaneously.

Research continues to show that a low percentage of individuals meet recommended physical activity guidelines throughout the world and that these statistics deteriorate as one transitions from childhood through adulthood and ageing.<sup>4</sup> These statistics worsen in the presence of various disease states.<sup>4,5</sup> Fundamental to most exercise recommendation statements is the advocacy for aerobic training (AER) and more recently, resistance training (RES).<sup>6</sup> Resistance training is an important addition to healthcare as the combination of modalities (AER+RES) may be equally, if not more beneficial to health in some cases.<sup>7,8</sup> In 2007, Sigal et al. demonstrated in the DARE Trial that AER+RES proved more beneficial for reducing HBA1c and some components associated with metabolic syndrome than AER alone.<sup>8</sup> However, the time commitment associated with AER+RES training in DARE (270 min/wk) may be more than most individuals are willing to adopt given the low rates of exercise participation observed in most countries.<sup>9</sup>

We recently reported in the HART-D Trial that an exercise intervention using the same treatment strategy as DARE, yet modelled for time commitment according to current exercise health recommendations, also demonstrated a greater reduction in HBA1c and increased maximal cardiorespiratory capacity ( $VO_{2peak}$ ) associated with AER+RES training.<sup>6,7</sup> Mechanistically, we have also shown that AER+RES training in HART-D significantly improved several aspects of skeletal muscle mitochondrial content and substrate oxidation.<sup>10</sup> While the primary outcome reports from DARE and HART-D examined various components of metabolic syndrome, neither study has undertaken an assessment of metabolic syndrome in its entirety. The analysis of metabolic syndrome is important given a recent report by Bateman et al. (2011) demonstrating that while RES training did not affect metabolic syndrome, AER and

AER+RES training decreased metabolic syndrome similarly in individuals who were sedentary, overweight, and dyslipidemic.<sup>11</sup> These factors combined are of primary importance to patient care for individuals with T2D. A secondary challenge to these types of investigations is the attempt to reconcile modest, yet potentially important differences, between epidemiologic reports and clinical trial outcomes.

Epidemiology trials examining maximal cardiorespiratory fitness (CRF) often report CRF in terms of Metabolic Equivalent Tasks or METs calculated at time-to-exhaustion (TTE) due the inability to measure respiratory gas exchange in large trials. Based on epidemiology findings it has been estimated that an improvement in 1 MET carries with it a 13-19% reduction in all-cause and cardiovascular (CVD) mortality risk, respectively.<sup>12,13</sup> We have recently demonstrated a dose dependent decrease in metabolic syndrome associated with fitness from the ACLS data set.<sup>14</sup> Despite the protective effects of fitness found in epidemiology, clinical exercise trials show a smaller effect when equating exercise findings using METs calculated directly from  $VO_{2peak}$  despite a more pronounced improvement in TTE within the same trial.<sup>7,15</sup> This disparity is important to consider as the true impact of clinical trials using  $VO_{2peak}$  as a “gold standard” may not be fully appreciated. While the differences between directly measured and estimated METs can be posited objectively to differences in actual versus estimated METs, it is also conceivable that the difference between changes in  $VO_{2peak}$  and TTE could be explained by improvements in exercise efficiency.

The primary of aim of this analysis is to examine participants in the HART-D cohort to determine the relationship between AER, RES and AER+RES training and metabolic syndrome in participants with T2D.<sup>7</sup> We hypothesize that metabolic syndrome will improve in a “dose-dependent” manner moving in order of effect from RES, to AER, to AER+RES training. Our secondary aim is to explore the relationship between metabolic syndrome and maximal fitness, whereby we propose that exercise efficiency will explain, in part, improvements in metabolic syndrome.

## **METHODS**

The primary aim of the HART-D trial (N=262) was to examine the effect of 9-months AER, RES and AER+RES training on HbA<sub>1c</sub> in participants with T2D.<sup>7</sup> Volunteers presented to HART-D as sedentary men and women (30-75 y) with T2D (HbA<sub>1c</sub> = 6.5% - 11.0%). We defined sedentary behavior as performing AER exercise < 20 minutes on < 3 days per week and not participating in RES. Individuals were

excluded for the presence of or medical history of stroke, advanced neuropathy or retinopathy, or other serious medical condition contraindicated for exercise or that may prevent adherence to the study protocol. The Pennington Biomedical Research Center institutional review board approved the HART-D study annually, and written consent was obtained from all participants prior to study screening. All study procedures were performed in accordance with the Declaration of Helsinki.

### *Study Design and Intervention*

Volunteers who met inclusion criteria were randomized to AER, RES, or AER+RES, or a non-exercise control group (Control). During the study, we maintained separate intervention and assessments teams and clinical testing and intervention laboratories were housed in separate buildings. During the course of the trial, participants met with a certified diabetes educator each month to track medication and health history changes and all exercise sessions were constantly monitored by trained study staff. The Control group was offered weekly stretching and relaxation classes. Participants randomized to the Control group were asked to maintain their normal daily physical activity level throughout the intervention. We confirmed physical activity levels using step counters. The stretching and relaxation classes were optional and considered light intensity physical activity inadequate to influence CRF or produce significant increases in strength. It should be noted, however, that during the course of the study, data safety monitoring procedures caused us to discontinue the Control group after a significant number of participants (~17%) had an increase in HbA<sub>1C</sub> > 1.0%, resulting in an unequal number of participants in the Control group.

The AER and AER+RES groups participated in treadmill walking 3 - 5 days per week at a moderate to vigorous intensity ( $65.4 \pm 14.6\%$  of peak oxygen consumption;  $\text{VO}_{2\text{peak}}$ , mean  $\pm$  SD). The exercise dose in the AER group was prescribed at 12 kcal per kg body weight per week (KKW), which was estimated to be equivalent to ~150 min/wk. Participants were weighed weekly to calculate the prescribed weekly caloric energy expenditure rate estimated from standard equations published by the American College of Sports Medicine.<sup>6,16</sup> The time required per session was calculated by dividing the weekly dose by the estimated caloric expenditure rate and the total number of sessions completed that week. The AER dose was lowered to 10 KKW in the AER+RES group to accommodate the RES component and ensure equal time commitment across all exercise groups.

The RES group completed 3 days of strength training exercises per week consisting of 2 sets of 4 upper body exercises (bench press, seated row, shoulder press, and lat pull down), 3 sets of 3 lower body exercises (leg press, extension, and flexion), and 2 sets of abdominal crunches and back extensions. Each set consisted of 10-12 repetitions and the amount of weight lifted was progressively increased once a participant was able to complete 12 repetitions on the final set of an exercise on 2 consecutive RES sessions. Participants in the AER+RES group completed 2 sessions of RES each week consisting of 1 set of 10-12 repetitions for all resistance exercises.

## **Measurements**

*Metabolic syndrome and Cardiorespiratory Capacity.* The primary outcome for our analysis is metabolic syndrome as defined by NCEP ATP III guidelines.<sup>1</sup> Cardiorespiratory fitness was evaluated using a standardized, ECG monitored, treadmill test while simultaneously collecting respiratory gases sampled from a True Max 2400 Metabolic Measurement Cart (ParvoMedics, Salt Lake City, Utah). From this test we measured peak oxygen  $VO_{2peak}$  and time-to-exhaustion (TTE), subsequently METs as (1) as  $VO_{2peak}$  in ml/kg/min divided by 3.5 and (2) according to ACSM calculations based on speed and grade obtained at the end of exercise testing.<sup>17</sup> Our rationale for examining  $VO_{2peak}$  and TTE is based on our desire to detail the clinical/physiologic changes surrounding  $VO_{2peak}$  and the epidemiological index of time-to-exhaustion, as well as ascertaining exercise efficiency (*detailed below*).

To examine exercise efficiency we first calculated ventilatory threshold 1 (VT1) using the v-slope method by plotting  $VO_2$  and  $VCO_2$  on the x- and y-axes, respectively, and visually examining the slope of the relationship for a breakpoint in linearity.<sup>18</sup> We also calculated the respiratory compensation point attained during each test as an increase in the ventilatory equivalent of oxygen ( $VE/VO_2$ ) and end-tidal partial pressure of oxygen ( $PET_{O_2}$ ) with no concomitant increase in the ventilatory equivalent of carbon dioxide ( $VE/VCO_2$ ) to confirm these findings. It should be noted that within the literature, respiratory compensation is also referred to ventilatory threshold 2 (VT2).<sup>19</sup> For consistency we will use VT2. To determine exercise efficiency, we calculated the slope of the line between the time of onset of VT1, VT2, and TTE.

## *Blood Chemistries and Anthropometric Measures*

Hemoglobin A<sub>1C</sub> (HbA<sub>1C</sub>) was obtained by venipuncture after a 10-h fast and analyzed with a Beckman Coulter DXC600 Pro (Brea, CA). Weight was measured on a GSE 450 electronic scale (GSE Scale Systems, Novi, Michigan) and height was measured using

a standard stadiometer. Body mass index was calculated as follow: body weight (kg)/height (m<sup>2</sup>). Waist circumference was measured to the nearest 0.1 cm at the level of the iliac crest while the subject was at minimal expiration. Body composition was measured by dual-energy x-ray absorptiometry using the QDR 4500A whole-body scanner (Hologic Inc., Bedford, MA).

### ***Statistical Methods.***

The primary outcome for our analysis is metabolic syndrome. For secondary outcomes we examined changes in respective metabolic syndrome component versus between the components features of metabolic syndrome (list them here?) and METs derived from VO<sub>2peak</sub> and TTE. For exploratory purposes, we also examined the relationship between exercise efficiency and metabolic syndrome. For our primary and secondary analyses we used a generalized linear model to analyse the influences of the differing doses of exercise training on metabolic syndrome (SPSS version 21.0, Somers, NY). Relationships for our tertiary analysis were performed using a Spearman correlation analysis for changes in metabolic syndrome versus changes cardiorespiratory fitness, metabolic syndrome components, and anthropometry indices as independent variables. For this latter analysis, we performed a bootstrap analysis of our data using 1,000 imputations. Bootstrapping was used in order to improve the accuracy of confidence intervals surrounding various correlations as we reasoned that (1) our cohort continued their medication use during the study and (2) owing to our original report, the participants in our study reduced medication use concurrent with exercise training.<sup>7</sup> Subsequently, any change in medication use surrounding metabolic syndrome components would likely influence our analysis effectively reducing the magnitude of the amount of changes in metabolic syndrome.

Based on our primary outcome paper, all of our analyses were covaried for age, ethnicity, duration of diabetes, baseline HbA1c, and baseline and follow-up medications used for diabetes, blood pressure, and cholesterol. We also included baseline metabolic syndrome score within this analysis. Within group differences between baseline and follow-up are reported as mean and 95% confidence intervals (95% CI). When we observed significant trends, we further explored our findings using *a priori* comparisons between each exercise-training group vs. the Control group via Dunnett-Hsu post-hoc assessments. All reported P-values are two-sided ( $P < 0.05$ ) and our report accounts for Dunnett-Hsu adjustments when reported. Data are presented as Mean  $\pm$  SD or mean change from baseline and 95% confidence intervals as appropriate.



## RESULTS

The demographic characteristics and clinical features of our cohort (N = 262) are presented in **Table 1**. For our exploratory analyses of exercise efficiency we successfully examined 207 participants who had complete data for each variable examined. No significant differences were observed for maximal fitness characteristics or percentage presenting with metabolic syndrome between the entire cohort and our tertiary assessment so we have presented all fitness characteristics in **Table 2**. Overall, participants presented with an average age of  $56 \pm 9$  y and diabetes duration of  $7.1 \pm 5.5$  y. Based on BMI ( $34.9 \pm 5.9$  kg/m<sup>2</sup>) participants in our study ranged from class I to class III obese.

Based on  $\text{VO}_{2\text{peak}}$  ( $20.1 \pm 4.3$  ml/kg/min) participants in HART-D were low fit, ranking in the lower 15<sup>th</sup> percentile for maximal cardiorespiratory capacity achieved during exercise testing.<sup>17,20</sup> [ENREF 15](#) These levels correspond to the Class I/II fitness levels as defined by the New York Heart Association.<sup>21</sup> Fifty-nine percent of our cohort presented with metabolic syndrome at baseline. Sixty three percent of our cohort were women, 44% black, 3% Asian and 0.5% Hispanic. Ninety-seven percent of our cohort used diabetes medications, 79% blood pressure medications and 64% cholesterol medications at baseline.

*Metabolic syndrome.* We have presented the results of our metabolic syndrome analysis in **Figure 1** where we observed a significant trend ( $P = 0.003$ ) for a decrease in metabolic syndrome within the AER (-0.49, 95% CI -0.77, -0.21) and AER+RES (-0.64, 95% CI -0.92, -0.35) groups. Both of these findings were significant ( $P \leq 0.02$ ) vs. Control (0.03, 95% CI -0.33, 0.40) and RES (-0.03, 95% CI -0.30, 0.24).

For our analysis of metabolic syndrome components, we observed a significant trend ( $P < 0.03$ ) for reduced waist circumference improvement for all treatment groups: RES (-1.91 cm; 95% CI, -3.03, -0.78), AER (-1.58 cm; 95% CI, -2.76, -0.39), and AER+RES (-2.80 cm; 95% CI, -3.93, -1.67), with all treatment groups being significant vs. Control (0.67 cm; 95% CI, -0.82, 2.15),  $P < 0.05$ ). We also observed a significant reduction in systolic blood pressure for the AER group (-6.61 mmHg; 95% CI -6.00, -0.22), also significant vs. Control ( $P < 0.05$ ). No other metabolic syndrome features were found to be significant.

*Maximal Cardiorespiratory Capacity.* Participants presented at baseline with an absolute  $\text{VO}_{2\text{peak}}$  of  $1.92 \pm 0.5$  L and relative  $\text{VO}_{2\text{peak}}$  of  $20.1 \pm 4.3$  ml/kg/min. This

equated to a measure maximal MET capacity of  $5.8 \pm 1.2$ . Time-to-exhaustion during treadmill testing was  $641 \pm 151$  seconds or approximately  $10.7 \pm 2.5$  minutes. This equates to  $8.57 \pm 1.3$  estimated METs. The mean METs measured from  $\text{VO}_{2\text{peak}}$  were  $5.75 \pm 1.2$  and significantly lower than METs estimated from speed and grade at TTE ( $P < 0.05$ ).

After 9 months of exercise training we observed a 5-6% increase in METs measured by gas exchange vs. a 25-30% increase in METs estimated from speed and grade. For measured METs, we observed minor; yet, significant increases in the AER and AER+RES training (**Fig. 2**). However, no between group differences were otherwise noted. For estimated METs, we also observed significant increases in the AER and AER+RES training groups that were (a) significantly different than measured METs and (b) significantly different than respective measured METs ( $P < 0.05$ ; **Fig. 2**).

METs obtained directly from  $\text{VO}_{2\text{peak}}$  were: Control (-0.09, 95% CI, -0.28, 0.11), RES (0.00, 95% CI, -0.14, 0.17), AER (0.14, 95% CI, 0.02, 0.28), AER+RES (0.29, 95% CI, 0.14, 0.42). METs calculated from speed and grade were: Control (-0.25, 95% CI, -0.66, 0.15), RES (0.12, 95% CI, -0.19, 0.42), AER (1.04, 95% CI, 0.71, 1.36), and AER+RES (1.30, 95% CI, 1.01, 1.61), with the AER and AER+RES being significantly greater than Control and RES ( $P < 0.05$ ).

Time-to-exhaustion following exercise training decreased in the Control group (-28 sec; 95% CI -76, 20) and showed a small increase for the RES (13 sec; 95% CI -23, 49) training group. Neither of these changes was statistically significant. However, a significant increase in TTE was observed for the AER (119 sec; 95% CI 81, 157) and AER+RES (154 sec; 95% CI 118, 189) training groups, with both being significant vs. Control and RES groups ( $P < 0.05$ ; **Fig. 3a**).

*Sub-maximal Cardiorespiratory Indices and Exercise Efficiency.* Similar observations to TTE were noted for the time-to-onset of VT1 (**Fig. 3b**) and VT2 (**Fig. 3c**). However, while VT1 improved in all treatment groups, VT2 improved only in the AER and AER+RES training groups compared to baseline. Specifically, VT1 (**Fig. 3b**) did not improve in the Control group (9.0 sec; 95% CI -29, 47), but significantly increased in all treatment groups: RES (51 sec; 95% CI, 5, 63); AER (34 sec; 95% CI 22, 80); AER+RES, (89 sec; 95% CI, 61, 117). For VT2 (**Fig. 3c**), no significant improvements were noted for the Control, (6 sec, 95% CI, -44, 56) or RES (28 sec; 95% CI, -11, 68)

groups, but were significant for the AER (91 sec; 95% CI, 50, 133) and AER+RES (163 sec; 95% CI 123, 203) groups (**Fig. 3b**). The net effect of these changes was a rightward shift in the slope of the relationship between from baseline to follow-up for VT1, VT2 and TTE where no significant improvements were observed for the Control group (**Fig. 3d**). The changes for the AER and AER+RES training groups were both significant vs. the Control and RES training groups ( $P < 0.05$ ). The net effect of these changes is schematically represented for the entire cohort in **Figure 4**. Lastly, our analysis showed significant correlations for changes between metabolic syndrome, TTE ( $r = -0.33$ , 95% CI -0.49, -0.15),  $VO_{2peak}$  ( $r = -0.24$ , 95% -0.36, -0.05), and waist circumference ( $r = -0.14$ , 95% -0.11, -0.40). No other significant relationships were noted for other indices of body anthropometry.

## DISCUSSION.

The primary findings from our current study show that AER and AER+RES training effectively reduce metabolic syndrome in individuals with T2D. Though the magnitude of treatment effects was not “dose dependent,” per se, the AER+RES training arm of our study did show a modest tendency for improvement larger reduction in metabolic syndrome score. This difference, however, was not statistically different. What is notable is that AER+RES performed in accordance with contemporary exercise guidelines as an effective strategy for reducing metabolic syndrome scores in individuals with T2D and should be considered as a viable treatment schema. When examined as individual metabolic syndrome component features, we also found that waist circumference was significantly reduced in all exercise groups, while systolic blood pressure was significantly reduced only in the AER group. No other significant component feature reductions were noted for metabolic syndrome. These findings are clinically important to individuals who present with T2D, low CRF, and metabolic syndrome simultaneously.

Previous research shows a greater CVD and all-cause mortality risk for individuals who have coexisting metabolic syndrome and T2D.<sup>2,3</sup> In 2006, Guzder et al. (2006) demonstrated that age, sex, smoking status, total cholesterol, antiplatelet therapy, antihypertensive therapy, and lipid lowering therapy adjusted survival curves in patients with conjoint metabolic syndrome and T2D exhibited a hazard ratio (HR) for incident CVD of 2.05 compared to individuals with T2D alone. Under the assumption that the presence of T2D qualified all participants with a minimum of one

metabolic syndrome feature, compounding risk was also observed for the accretion of two (HR,  $1.93 \pm 0.39$ ), three (HR  $2.71 \pm 0.18$ ), four (HR,  $4.23 \pm 0.56$ ), and five (HR,  $4.76 \pm 0.042$ ) metabolic syndrome component features. Najarian et al. (2006) have also shown in data obtained from the Framingham Study that the relative risk of stroke in individuals with diabetes and metabolic syndrome is approximately 32%-55% higher than those individuals presenting with diabetes or metabolic syndrome alone.<sup>3</sup> Previous reports from our group in men show similar findings.<sup>22</sup> In a prospective report from the Aerobics Center Longitudinal Study, we found that CVD deaths were higher in individuals with diabetes alone (5.5/1,000 man years; HR; 2.9, 95% CI 2.1–4.0) and in combination with metabolic syndrome (6.5/1,000 man years; HR; 3.4 95% CI 2.8–4.2) vs. men without diabetes or metabolic syndrome (1.9/1,000 man years) or metabolic syndrome only (3.3/1,000 man years; HR; 1.8, 95% CI 1.5–2.0).<sup>22</sup>

Epidemiology trials also demonstrate that AER and RES are inversely and independently associated with metabolic syndrome.<sup>14,23,24</sup> While clinical exercise intervention trials also support the efficacy of AER or RES training for reducing metabolic syndrome, less is known about combining AER+RES training, especially for those presenting with T2D and metabolic syndrome. A difficulty in interpreting the current literature with regard to the RES training aspect of metabolic syndrome is a relative paucity of trials examining RES training on metabolic syndrome versus examining the role of RES on the individual component features of metabolic syndrome. This difficulty is exemplified in a recent systematic and meta-analysis by Strasser et al. (2010), who examined 13 trials involving RES and metabolic syndrome. While the authors provided an excellent review of RES training on the *component features* of metabolic syndrome they did not, or were unable to, account metabolic syndrome as a composite score. Fewer reports still have examined the effect of AER+RES training in metabolic syndrome.

Similar in nature to HART-D, Sigal et al. reported in the DARE trial, significant reductions in HBA1c coinciding with AER, RES and AER+RES training.<sup>8</sup> Despite the reporting of metabolic syndrome composite features, no further analysis was undertaken to examine metabolic syndrome itself. To date, only the study of Bateman et al. (20011) have examined the effects of AER+RES on metabolic syndrome in participants from the STRIDDE study.<sup>11</sup> Though STRIDDE did not examine individuals with T2D, they demonstrated similar effects to our current report in a convenience sample of 84 out of 196 individuals presenting with all five NCEP ATP

III defined metabolic syndrome components. Specifically, participants partaking in AER and AER+RES training decreased metabolic syndrome, while those undertaking RES and Control conditions showed no reduction. Overall, the findings of HART-D and STRIDDE demonstrate that AER and AER+RES training are equally effective for reducing metabolic syndrome in T2D and non-diabetic individual, respectively.

Mechanistically, the effects of exercise on metabolic syndrome are related to changes in a number of physiologic and cardiovascular adaptations to exercise training. Physiologically, the effects of exercise training on the component features of metabolic syndrome have been thoroughly reviewed elsewhere and are not elaborated on here.<sup>(ref)</sup> However, an underlying question we posed when undertaking our current analysis was to examine potential differences between clinical trials that rely on laboratory measure of  $VO_{2peak}$  and epidemiologic trials that typically use TTE and corresponding MET values. One of the features we observed in some of our trials, inclusive of HART-D, was a disparity between the relative increase in measured  $VO_{2peak}$  and TTE.<sup>(ref)</sup> In our current analysis, we observed a significant difference between MET values measured from  $VO_{2peak}$  (5-6%) and TTE (25-30%), with the latter showing a stronger relationship with metabolic syndrome. It is easy to rationalize this apparent inequality in terms of the mathematical variance associated with estimating METs from an equation based on speed and grade versus the actual measurement of  $VO_{2peak}$ . This disparity, however, makes it difficult to reconcile epidemiology and clinical trials as data from epidemiology trials suggest a 13% and 15% reduction in all-cause and CVD risk mortality, respectively, for each MET attained during exercise testing.<sup>13</sup> Rather than assume that the difference between the two measures was simply a matter of the mathematical variance introduced with prediction equations, we hypothesized that some of this disparity could be explained by improvements in exercise efficiency.

Our findings showing significant, yet higher correlations for TTE and  $VO_{2peak}$  are intriguing. Though both measurements detail “maximal cardiorespiratory capacity,” per se and may covary to some degree, they also reflect differences in the physiologic response to graded exercise testing. While  $VO_{2peak}$  reflects changes in measured cardiorespiratory capacity, which, in and of itself is a reflection maximal cardiac output and muscle oxygen utilization, TTE may reflect an improvement in sub-maximal exercise efficiency. Unfortunately, little data exists examining this relationship. Numerous methods have been proposed to measure exercise efficiency in athletic and

clinical populations including mechanical efficiency, gross efficiency, delta efficiency, oxygen uptake efficiency slope, and others.<sup>25-29</sup> While all of these methods have their strengths and weaknesses, each measure is largely dependent on a single point of observation or the slope of the changing relationship between the oxygen uptake of sequential stages, and hence, the workload involved in exercise testing.

In a classic experiment, Beaver et al. (1986) demonstrated that “anaerobic threshold” could be determined by the ventilatory threshold or V-slope method, which examines the departure from linearity between carbon dioxide (VCO<sub>2</sub>) and oxygen uptake (VO<sub>2</sub>).<sup>19</sup> In the same study, the authors also describe a second break point occurring in the latter stages of exercise testing between minute ventilation (V<sub>e</sub>) and VCO<sub>2</sub>. For simplicity we will hereafter refer to these break points as VT1 and VT2, respectively, where VT1 represents the first rise in blood lactate concentration leading to a disproportionate increase in carbon dioxide<sup>30,31</sup> and VT2 due to a respiratory compensation reflecting an exercise induced hyperventilation and an increase in minute ventilation relative to carbon dioxide.<sup>26,27,18</sup> For our analysis we examined the slope of the relationship between VT1, VT2 and maximal exercise, finding that the slope of this relationship improved in the AER and AER + RES groups and that these changes were more strongly related to TTE than measured VO<sub>2peak</sub>. From these data, we conclude that exercise training improves the underlying physiology encumbered during exercise testing and that these improvements equate to an improvement in TTE, and subsequently, partially explain the difference between estimated METs vs. those obtained from laboratory derived VO<sub>2peak</sub>.

A primary strength of HART-D is that it was a highly controlled clinical exercise intervention lasting 9-months. Our study is limited in its generalizability to those with T2D. Still, findings from STRIDDE suggest that the findings are similar in those without diabetes. It might also be argued that the degree of medical supervision (i.e., prescriptive medications) surrounding our cohort could introduce uncontrollable statistical variance into our reported outcomes. From a clinical perspective, we have accounted for changes in medication within our statistical analysis by using baseline and follow-up medication use. This, in turn, strengthens our findings, as they are standard measures of clinical care and patient healthcare management. One of the strongest features of our study is that it was designed to emulate current public guideline statements for exercise. Taken in combination our results show that AER or AER+RES

training plays an important role in the management of individuals with T2D who also present with sufficient qualifying components to also have metabolic syndrome.

## **Disclosures**

Dr. Church receives honoraria for lectures from scientific, educational, and lay groups. Dr. Church has a book entitled “Move Yourself: The Cooper Clinic Medical Director’s Guide to All the Healing Benefits of Exercise.” Dr. Church has received research funding from the American Heart Association and the National Institutes of Health as well as unrestricted research funding from Coca-Cola. Dr. Church has overseen study sites for large pharmaceutical trials funded by Sanofi Aventis, Orexigen, Arena and Amylin. Dr. Church is a member of the Jenny Craig Medical Advisory Board and has served as a consultant to Technogym, Trestle Tree, Vivus, Lockton-Dunning and Neuliven Health. In addition, he serves as the Senior Medical Advisor for Catapult Health

No other disclosures are otherwise noted.



## FIGURE LEGENDS

**Figure 1.** Represents changes in categorical metabolic syndrome scores from baseline to follow-up. Data are Mean  $\pm$  95% CI. Statistical significance is noted as: <sup>a</sup> Aerobic vs. Control, P = 0.028; <sup>b</sup> Aerobic vs. Resistance, P = 0.02; <sup>c</sup> Aerobic+Resistance vs. Control, P = 0.005; <sup>d</sup> Aerobic+Resistance vs. Resistance, P = 0.003.

**Figure 2.** Data represent changes in waist circumference and systolic blood pressure from baseline to follow-up. Data are Mean  $\pm$  95% CI. Statistical significance is noted as: <sup>a</sup> Aerobic vs. Control, p = 0.028.

**Figure 3.** Data represent changes in diastolic blood pressure, fasting glucose, triglycerides and HDL-C from baseline to follow-up. Data are Mean  $\pm$  95% CI.

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